Regulatory requirements for genetically modified organism (GMO) applications: tips and tricks for global ATMP and vaccine development

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Genetically Modified Organisms (GMOs)

In the EU, a GMO is defined as an organism in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination (Directive 2001/18/EC). Investigational Medicinal Products (IMPs) containing or consisting of GMO include ATMPs (GTMPs) and vaccines, and in some cases, plasmids (such as The Netherlands).

GMO regulation hurdles

EU clinical trial applications (CTAs) and marketing authorisation applications (MAAs) containing or consisting of GMOs require licenses for use.

Two GMO Directives are applicable:

- 2001/18/EC on the deliberate release into the environment of genetically modified organisms (DR)
  "Deliberate release" means any intentional introduction into the environment of a GMO or a combination of GMOs for which no specific containment measures are used to limit their contact with and to provide a high level of safety for the general population and the environment.
- 2009/41/EC on the contained use of genetically modified micro-organisms (CU)
  "Contained use" means any activity in which microorganisms are genetically modified or in which such GMMs are cultured, stored, transported, destroyed, disposed of or used in any other way, and for which specific containment measures are used to limit their contact with, and to provide a high level of safety for, the general population and the environment.

CU is usually for the site, and DR for the CT, but not always.

This implies that the interpretation and application of the legislation is variable among EU Member States (MS) creating an administrative burden requiring a separate GMO notification in each MS.

In the U.S. a "claim of categorical exclusion" can be requested implying that no environmental risk analysis (ERA) has to be provided, unless 21 CFR 25.21 (extraordinary circumstances) is implemented (example: replication-competent virus with a novel tropism and/or species specificity).

Key requirements for GMO license requests

Through the extensive expertise of Asphalion in GMO notifications, these key insights are highlighted for CTAs.

1) Prepare information
   - Site specific: cleaning procedures, storage of GMO, internal transport of GMO and samples, flow of GMO and samples (Figure 2).
   - CMC: manufacturing, Quality Control, vector maps, sequencing, homology evaluations.
   - NC: Biodistribution and shedding of GMO.

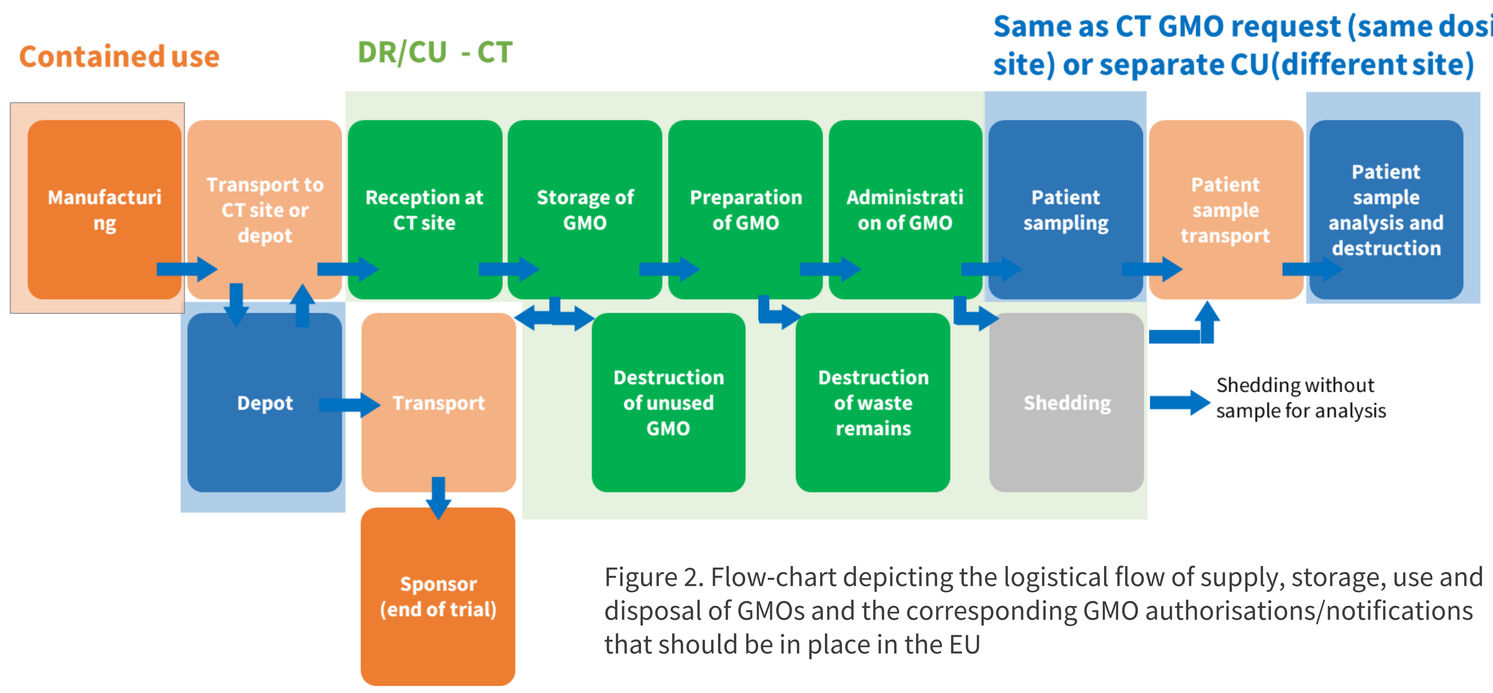

Figure 2. Flow-chart depicting the logistical flow of supply, storage, use and disposal of GMOs and the corresponding GMO authorisations/notifications that should be in place in the EU

2) Identify the country/ies legal basis and the timing for GMO vs CTA (Figure 1).
3) Due diligence on potential clinical sites/PI, taking into account their experience in GMOs.
Identify the Biosafety Officer (BSO) at the clinical site: main contact point.
4) Identify the technical and administrative documents required for each country.
   - For rAAVs or CAR T-cells, most of EU countries accept a Common Application Form.
   - ERA – Environmental Risk Assessment: Annex II of Directive 2001/18/EC; Decision 2002/623/EC; Directive 2018/350.
   - SNIF – Summary Notification Information Format: Directive 2001/18/EC; Decision 2002/813/EC.

   Consider that some documents may be public and would affect Intellectual Property.
5) Check for import/export authorisation requests (GMO/IMPs, biological samples), and fees.
6) Estimate submission and decision dates according to local deadlines and CTA plan.
7) Generate a Master GMO document with a profound environmental risk analysis, including confidential information.

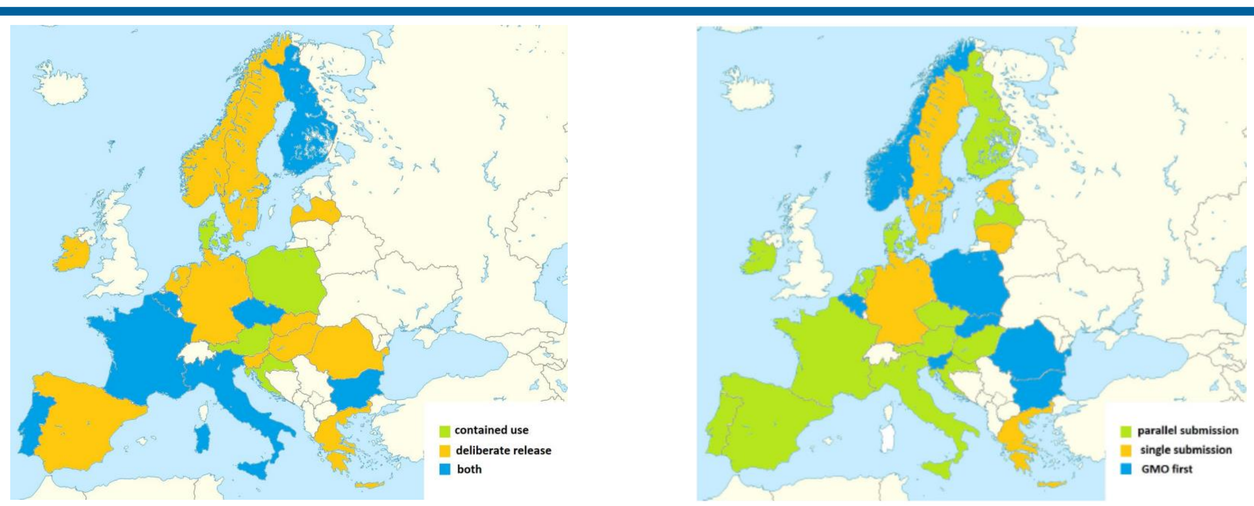

Figure 1. EU Legislation for GMOs in Clinical Trials (Tomas Boran, State Institute for Drug Control, CAT Industry Interested Parties Meeting, 2021)
Left: Directive/s applied in each EU Member state
Right: Timing for GMO submission/approval in relationship to CTA

The future of GMO in the EU

The current GMO scenario in the EU, which is not harmonised, leads to delays to clinical trials with ATMPs, and positions the EU at the rear-guard of the investigation in innovative therapies such as ATMPs and vaccines which consist of or contain GMOs. In addition, extremely confidential information (such as manufacturing and quality control data) has to be shared with third-parties as clinical sites, leaving Sponsors in an unpleasant position.

Clinical Trials Regulation (CTR) 536/2014/EU entered in force in 2014, but its application started the 31st of January 2022. With the CTR, the Clinical Trials Information System (CTIS) was introduced. This is an EU CTA submission portal and database that facilitates a single CTA submission via a single EU portal, and an integrated assessment procedure leading to a single decision. However, EU missed the opportunity to consolidate GMO Regulations together with CTA, and to leverage EU in the GMO clinical area.

Finally, the EU pharmaceutical legislation is currently being reformed, and will impact the GMO scenario in the EU.

Regulatory, Scientific & Safety Consulting in Life Sciences

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Asphalion has participated in the following research projects funded by the European Union's Horizon 2020 Research and Innovation programme: MISTRAL-HIV (No 847943), CardioReGenix (No 825670), RBDCOV (No 101046118), and UroPrint (No 964883); and on the Innovative Medicines Initiative 2 Joint Undertaking project ARDAT (No 945473), and on the Eurostars project Synchropace (ref. 115484 through the Innovative UK Project 600538).